A phase 2 study of the OX40 agonist BGB-A445, in combination with docetaxel or BGB-15025, an HPK1 inhibitor, in patients with NSCLC pretreated by anti-PD-(L)1 antibodies

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Background: OX40, an immune co-stimulatory receptor mainly expressed on activated T cells, plays a role in T-cell survival, proliferation, and proinflammatory cytokine expression. BGB-A445 is a novel mAb agonist against OX40 with high specificity and affinity that showed preclinical antitumor activity. BGB-A445 preserves binding of OX40 to its endogenous ligand, reducing the hook effect (antibody excess) seen with other OX40 agents and maximizing antitumor activity. HPK1 is a negative regulator in antitumor immunity. Preclinical studies of BGB-A445 in combination with the HPK1i BGB-15025 show potentially enhanced antitumor effects. We report results from Part 1 of a ph 2, randomized, open-label, multicenter trial of BGB-A445 plus docetaxel or BGB-15025 in previously treated NSCLC pts (NCT06029127).

Methods: This trial was conducted in China and South Korea. In Part 1, pts were randomized to BGB-A445 in combination with docetaxel (Arm A) or BGB-15025 (Arm B). Eligible pts were ≥18 with advanced/metastatic NSCLC without actionable genomic alterations and ≤2L of prior systemic therapies, which must have included anti-PD-(L)1 treatment and a platinum-based CT. Primary endpoint was ORR; secondary endpoints were safety/tolerability, DOR, DCR, CBR, PK, and host immunogenicity; exploratory endpoints were biomarkers and PFS.

Results: As of Jul 1, 2024, 21 pts were randomized to Arm A and 14 to Arm B. In Arms A and B, respectively, median (range) ages were 65.0 (38.0–74.0) and 60.5 (45.0–79.0); 23.8% and 14.3% were female; 61.9% and 57.1% had squamous cell carcinoma. Median exposure to

BGB-A445 was 2.7 mo in A and 1.4 mo in B. Median study follow up was 3.2 mo in A and 3.3 mo in B.

There were no confirmed responses. In Arms A and B, respectively, DCR (95% CI) was 71.4% (47.8–88.7%) and 21.4% (4.7–50.8%); CBR was 9.5% (1.2–30.4) and 0% (0–23.2); median PFS was 2.8 (1.8–4.3) mo and 1.4 (1.2–1.4) mo. Low expression of OX40 in tumor tissue may contribute to lack of efficacy.

TEAEs occurred in most pts, with 66.7% in A and 7.1% in B having gr ≥3 TEAEs (**Table**). Most common gr ≥3 TEAEs in A were neutrophil count decreased and WBC count decreased; two gr 3 TEAEs (pneumonia; hypertension) occurred in the same pt in B. In both Arms, there were no TEAEs leading to death or discontinuation and no gr ≥3 imAEs. The most common (≥2 pts) imAE was rash.

Conclusion: BGB-A445 plus docetaxel or BGB-15025 was generally well tolerated in pts with advanced NSCLC and showed limited antitumor activity.

Safety

	Arm A BGB-A445 + docetaxel (N=21)	**Arm B BGB-A445 + BGB-15025 (N=14)**
Any treatment-emergent AE	20 (95.2)	12 (85.7)
Gr ≥3	14 (66.7)	1 (7.1)
Serious	7 (33.3)	1 (7.1)
Any treatment-related treatment-emergent AE	20 (95.2)	11 (78.6)
Gr ≥3	14 (66.7)	1 (7.1)
Serious	5 (23.8)	0
Any immune-mediated AE	3 (14.3)	4 (28.6)
Infusion-related reactions	4 (19.0)	1 (7.1)

Pts with multiple AEs are counted once. All AEs are n (%).